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CoxRival®

The use of CoxRival® to Control Coccidiosis in Poultry

Dr.Rapeewan Thampaisarn
Faculty of Veterinary Science, Thailand Mahidol University
DVM. Ekkachai Thanaphongphaisan
Vet Product R&D Centre. Bio Business Line. CP Group

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Introduction

Avian coccidiosis is an important parasitic disease in poultry production, caused by the intestinal protozoan parasites of the genus Eimeria. Eimeria spp. are highly specific to a susceptible host. Nine species are recognized to infect chickens (E. acervulina, E. brunetti, E. maxima, E. mitis, E. necatrix, E. praecox, E. hagani, E. mivati and E. tenella). Each of them multiplies in the preference part of gastrointestinal tract and causes tissue damage resulting in intestinal hemorrhage and diarrhea, leading to high mortality rates. Most of the infections are subclinical with no obvious clinical sign. Chickens will not die but still suffer from inefficient feed utilization and malabsorption. Consequently, they have poor growth performance. More importantly, they still shed the oocyst of eimeria into the environment (Quiroz-Castañeda & Dantán-González, 2015). Economic impact from coccidiosis is not caused by production loss only but also by costs of treatment and prevention. For poultry industry, global economic losses from coccidiosis are estimated to be up to $3 billion per year (Kadykalo et al., 2018).

Coccidiosis control strategy

Due to the persistent characteristic of oocyst in harsh environment conditions and disinfectants, good management and hygiene are still not capable to eradicate oocysts from the poultry house. Therefore, anticoccidial drugs have been used to control coccidiosis in chicken production as a preventive medicine known as chemoprophylaxis.

Based on mode of actions, the anticoccidial drugs can be classified into two categories; chemicals and polyether ionophores. Chemicals or synthetic compound affect parasite via disturbing parasite metabolism. For example, amprolium, clopidol, halofuginone, decoquinate. Polyether ionophores or ionophores kill parasite by disrupting ion balance of cell. Ionophores also were grouped into three sub-categories; monovalent ionophores (monensin, narashin and CoxRival®Salinomycin); monovalent glycosidic ionophores (maduramicin and semduramycin); divalent ionophores (lasalocid) (Peek & Landman, 2011) .

A myriad of ways has been proposed to replace the administration of anticoccidial drugs in feed such as vaccination, pre/probiotic, essential oils, steroids, yeasts, organic minerals, and plant extract. A large number of studies were done to evaluate anticoccidial activity in these alternative products. Some products were effective in vitro. However, the active substance, mechanisms and the consistent efficacy were still need more investigation and the applicable use in practical was still questioned. Live coccidiosis vaccines are available but mostly used for coccidiosis prevention in breeding flocks and laying hens. Due to the risk of causing clinical signs and high cost of production, the use of live vaccine in broiler is still considerable (Kadykalo et al., 2018). According to these condition, the use of anticoccidial drugs still play a major role in controlling of coccidiosis, especially in broiler production.

Brief history of Salinomycin

istory of Salinomycin

In 1973, salinomycin was isolated from the culture broth of Streptomyces albus (Kinashi et al., 1973). It was proved to have activity against gram-positive bacteria and some fungi. During that time, the former polyether ionophore antibiotics (monensin, lasalocid) were reported to be effective in the treatment of coccidiosis. Consequently, many studies were also conducted to evaluate an anticoccidial activity of salinomycin in chickens. Various concentrations of salinomycin in feed were investigated and a level of 60 ppm was determined to treat coccidiosis successfully (Migaki et al., 1979). Comparisons of anticoccidial activity between salinomycin, monensin and lasalocid in different condition (battery trials, floor-pen trials, and field trials) showed that the efficacy of salinomycin was comparable or superior to monensin and lasalocid. Using salinomycin gave advantages in the term of efficacy and body weight gain (Migaki et al., 1979; Chappel & Babcock, 1979). After safety evaluation of salinomycin in chickens was done and the Scientific Committee on Animal Nutrition (SCAN) issued an opinion on the use of salinomycin sodium in feedingstuffs for chickens in 1982, the commercial product was legally released to market (EFSA, 2004). Since then, salinomycin has been widely used to control coccidiosis in poultry production worldwide. Besides chickens, salinomycin is also authorized for the use in rabbits for fattening. Over the past few years, it was acknowledge to have anti-cancer effect and may be potentially used as a novel anti-cancer drug for human (Zhou et al., 2013).

Structure of CoxRival® salinomycin

CoxRival®salinomycin is a polyether carboxylic acid ionophore that exerts both antimicrobial activity against Gram-positive bacteria, some fungi and anticoccidial activity. It is produced from a fermentation of Streptomyces albus. The form of salinomycin sodium (Sal) is commercially used as an active substance. The IUPAC name of salinomycin sodium is ethyl-6-[5-{2-(5-ethyltetrahydro-5-hydroxy-6-methyl-2H-pyrano-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro [4,1,5,3] pentadec13-en-9-yl} 2-hydroxy-1,3-dimethyl-4-oxoheptyl] tetrahydroxy-5-methyl-2H pyran-2-acetic acid, sodium salt (C42H69O11Na) and the structural formula is shown in figure 2 (CAS Number 55721-31-8) (EFSA, 2016).

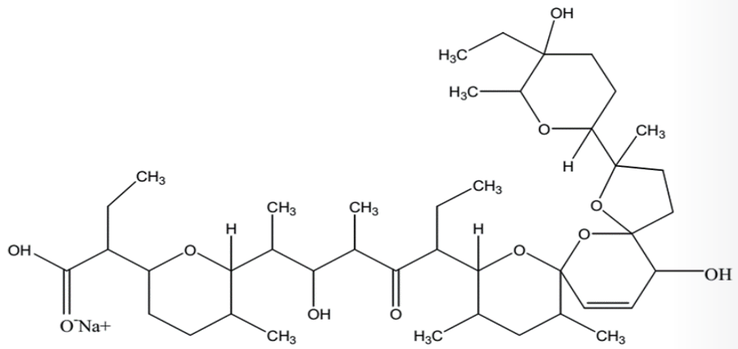

Fig 1. Structure of Salinomycin sodium

Mode of action

CoxRival®salinomycin is effective against coccidia in asexual stage (sporozoites and merozoites) which occur in the lumen of intestines.Sporozoites fail to become trophozoites. Merozoites fail to become gametes and the development of schizont is also impaired (Chappel, 1979). With a carboxyl group on one side of the molecule and two hydroxyl groups on the other side, CoxRival®salinomycin can form “head to tail” type of intramolecular hydrogen bonds resulting in formation of a pseudo-cylcic structure. The structure is able to form lipid soluble complexes with metal cation, particularly potassium ions (K +) in the gut lumen and transports them across lipid cell membrane of protozoa. In order to maintain intracellular ion concentration, protozoa constantly pump K+ out of the cell, but ionophores still facilitate K+ back to the cell again and again. Finally, the protozoa runs out of energy.Then, osmotic pressure in protozoan cell increases, leading to cell swelling and rupture (Antoszczak et al., 2014).

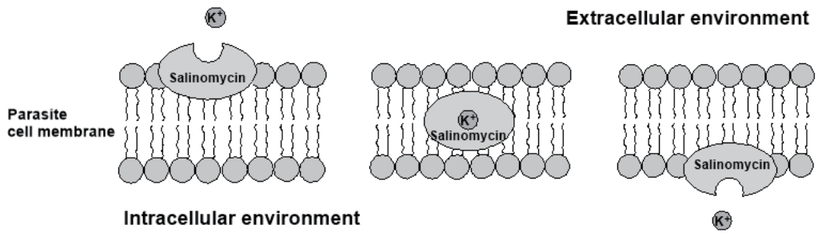

Fig 2. The transfer of cation into parasite cell by salinomycin

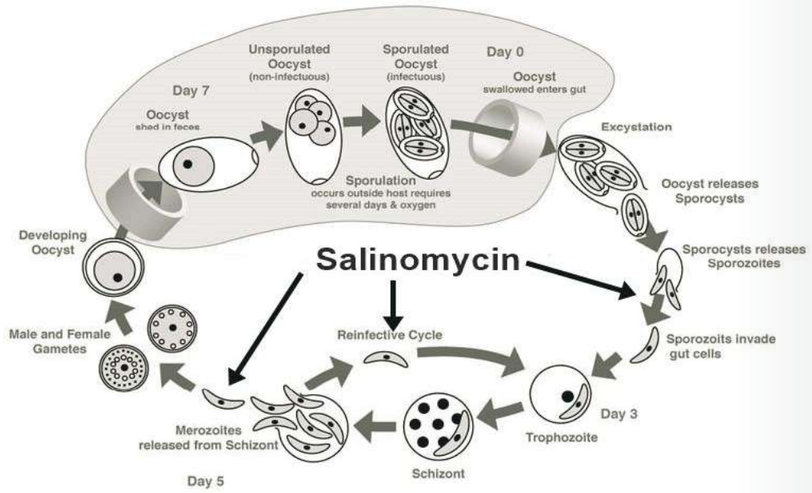

Fig 3. The life cycle of eimeria is illustrated. Salinomycin affect asexual stage development of Eimeria spp.

Pharmacokinetic and drug distribution

CoxRival®Salinomycin can be absorbed, distributed and excreted in the body of chicken rapidly. The pharmacokinetic of CoxRival® in chickens was done by many research groups. The parameters from each study is various, depending on experimental designs and analytical methods. However, most of the results are on the same pace as the others.

The kinetic of CoxRival® in chicken was evaluated with an administration of a single dose of CoxRival® (20mg/kg bodyweight) via oral and intravenous route. Thin layer chromatographic (TLC) assay was used to estimate quantity of CoxRival® in blood and tissue samples. The kinetic parameters from intravenous injection route can be described by a two-compartment open model with an absorption half-life of 0.5 h, an elimination half-life of 2.2 hours (h), a volume of distribution at steady state (Vdss) of 3.3 litre/kg. For oral route administration, the mean peak concentration of drug was reached at 0.37 hour with an absorption half-life of 0.2 h and elimination half-life of 1.96 h. The systemic bioavailability percentage was 73.02 %, indicating a high absorption from this route. The concentrations of CoxRival® in other tissues were reached the highest level within 2 h. The highest concentration was found in the liver, followed by kidneys, muscles (thigh and breast), fat, heart, and skin and it was still detected in liver, kidney, and fat 24 h after ingestion. No CoxRival® residues were detected in tissues after 48 h except in liver (0.1ug/g). CoxRival® concentrations in serum and tissues following admistration of 60 mg/kg feed for 14 days were lower than those after administration of a single oral route. The highest level of CoxRival® was also found in the liver but no residues were detected in all tissues after 48 h (Afef et al., 1993).

In another study, an ELISA was developed to detect CoxRival® in chicken tissues after feeding of medicated feed containing 60mg/kg CoxRival®. CoxRival® residues were excreted from plasma rapidly. Low concentrations of CoxRival® were detected in liver and muscle. The residues fell below the limit of detection by the assay within 2 days of withdrawal of the medicated feed.

To identify CoxRival® metabolites in chicken excreta and tissue more precisely, salinomycin labelled with 14C on carbon atoms of the molecule was used to track salinomycin derivatives. The metabolic fate of [14C]-salinomycin sodium (labelling position not given) was studied in chickens. Seventeen metabolites were identified by Liquid chromatography–mass spectrometry (LC-MS) analysis consisting of two isomeric diketo-monohydroxy-salinomycin, six isomeric dihydroxy-salinomycin, for isomeric trihydroxy-salinomycin, tetrahydroxy-salinomycin, two isomeric monoketo-monohydroxy-salinomycin, and two isomeric dihydroxy-monoketo-salinomycin.

Table 1. Kinetics of total residues concentration (TRC) and Marker residue (SAL) in chicken tissues after oral administration of 14C- CoxRival® equivalent to 70 mg/kg feed.

Withdrawal time (animals)	Liver		Kidney		Muscle		Skin/Fat	
	TRC	SAL*	TRC	SAL	TRC	SAL	TRC	SAL
1 h	1.487	0.087	0.183	0.027	0.027	0.008	0.156	0.087
3 h	0.987	0.031	0.144	0.005	0.021	0.004	0.164	0.067
6 h	0.391	0.005	0.077	0.002	0.012	0.001	0.060	0.011
24 h	0.194	<LOD	0.055	0.001	0.006	<LOD	0.045	0.001

*SAL determined by radio-HPLC and LOD reported <0.001 to 0.004 mg/kg

In order to assess CoxRival® total residue concentration (TRC), the study was carried out in broilers. They were administered 14C-salimonycin by gavage for seven consecutive days at a rate nominally equivalent to the highest dosage recommended for complete feed (70 mg/kg diet). They were sacarificed at different withdrawal time (1, 3, 6, and 24 hr after the last administration). The highest TRC was measured in the liver followed by the kidney, skin/fat and muscle, respectively (Table 1). Ho wever, depletion from the tissues was rapidly. At six h, very low concentration of CoxRival® were detected in the tissues and fail below the limit of detection (0.001-0.004 mg/kg) at 24 hr (EFSA, 2017). This result was similar to a previous assessment in 2004. Although chickens were overexposed with 140% of the target dose of 70 mg/kg feed, CoxRival® was not detectable at 0.25-day withdrawal period (EFSA, 2004).

Efficacy of CoxRival® salinomycin

Since the discovery of salinomycin in 1973, many publications reported the activity of salinomycin against Eimeria infection in chicken intestines. Efficacy data was provided based on studies conducted on three conditions; controlled battery-cage studies, controlled floor-pen studies, and controlled field trial. Major parameters were measured to evaluate salinomycin efficacy, including weight gain, oocyst shedding, intestinal lesion score, and mortality. In battery-cage studies, infection with a single species and a mix of six species were used to determine effective level of salinomycin. At the dose range from 12.5 to 50 ppm, using the higher dose in feed reduced mortality greater than using the lower dose (Table.2). The mortality rate in infected chickens was reduced to 0% when the dose over 50 ppm of salinomycin were added to chicken feed (Danforth et al., 1977a). Danforth et al. (1977b) also confirmed the efficacy of salinomycin in floor-pen studies. All dosed of salinomycin (60, 80, 100 ppm) significantly reduced coccidiosis-induced mortality rate in chicken which is similar to that of battery-cage study. In another battery-cage study, the dose of salinomycin at 60 ppm in feed exhibited excellent anticoccidial activity in chickens by improving lesion score and reducing mortality rate from coccidiosis (Migaki et al., 1979). Furthermore, to assess salinomycin efficacy under commercial poultry production, field trials were conducted in the United States. Used litter from farms in which coccidiosis had been recently diagnosed was used as a source of coccidian oocysts. In this study, moderate outbreak occurred only in the trial conducted in Maine. Even though no mortality from coccidiosis presented, intestinal lesion score observed in necropsied chickens given salinomycin (0.01) was significantly lower than unmedicated chickens (0.72) (Chappel & Babcock, 1979). Anticoccidial efficacy of salinomycin in chickens under different conditions was summarized in Table 3.

Table 2. Mortality rate of chicken infected with a single species and mixed species of Eimeria in battery trials

Treatment	Mortality rate (%)	
	E. tenella infection	Mixed Species infection
Unmedicated	8	50
CoxRival® salinomycin 12.5 ppm	5	45
CoxRival® salinomycin 25 ppm	10	28
CoxRival® salinomycin 50 ppm	8	0
CoxRival® salinomycin 75 ppm	0	0

Experimental condition	Route of oocyst exposure	Eimeria spp.	Dose of CoxRival® in feed	% mortality	Feed conversion ratio, age of chicken
Battery cage	oral inoculation	E. tenella	Unmedicated	23	2.04, 14 days
			60	0	1.84, 14 days
			80	0	1.81, 14 days
			100	0	1.86, 14 days
Floor pen	oral inoculation and floor-fecal seeding	mixed species	Unmedicated	2	1.72, 4 weeks
			60	0	1.66, 4 weeks
			80	0	1.67, 4 weeks
			100	0	1.63, 4 weeks
Battery cage	oral inoculation	Mixed species	Unmedicated	25.3	nd
			30	1.1	nd
			60	0.7	nd

After the efficacy studies was conducted in several conditions, the result concluded that CoxRival®concentration at 60 mg/kg feed was achieved to control coccidiosis and improve growth performance in chickens whereas a significant depression in feed intake and body weight was observed after dose higher than 77 ppm. According to Regulation No (EC)1831/2003, salinomycin sodium is authorized for use as a coccidiostat in chickens with a dose range from 50 to 70 mg/kg complete feed (Table 4.).

Table 4. Authorized maximum content of CoxRival® in complete feed

Active substance	Target animal	Authorized maximum content
Salinomycin sodium	Chickens for fattening (broilers)	70 mg/kg
	Chickens reared for laying (up to 12 weeks)	50 mg/kg

Occurrences of Eimeria spp. resistance to anticoccidial drug has been developed after an extensive use of anticoccidial drugs in poultry production for long time. The level of drug resistance is different in each geographical area. Therefore, re-evaluations of drug efficacy have been conducted in chicken using field strains isolated from their different country in the last decade (Table 5.).

In Thailand, field isolates of Eimeria spp. were used in the study of CoxRival® efficacy. Using CoxRival® alone at 70 ppm and a combination with robenidine (16.5 ppm and 33 ppm) significantly reduced lesion score compared to the infected unmedicated control chickens. Interestingly, the mixture of salinomycin (70 ppm) and decoquinate (20ppm) showed a better result with no gross lesion observed in infected chickens (Kaewthamasorn et.al, 2015).

Floor pen studies conducted in Europe (Spain and Lithuania) showed that the minimum dose of salinomycin at 50 ppm was effective in the control of coccidiosis in broilers by reducing lesion score and mortality rate. Moreover, it also improved body weight gain and feed conversion ratio (FCR) (EFSA, 2017). On the other hand, reduced sensitivity to salinomycin by E. acervulina and E. maxima was observed in Algeria. In this study, salinomycin was achieve to reduce lesion score and mortality rate better than un-medicated infected control group but it failed to improve weight gain and FCR (Djemai et al., 2016).

Table 5. Summary of efficacy studies of CoxRival® to control coccidiosis in chickens conducted in different regions of the world

Country	Eimeria spp.	Dosage (ppm in feed)	Efficacy result
Thailand	Mixed species	70 ppm	susceptible
		70 ppm+ robenidine 16.5 ppm	susceptible
		70 ppm +robenidine 33 ppm	susceptible
		70 ppm+ decoquinate 33 ppm	susceptible
Algeria	E.acervulina ,E. maxima	60 ppm	Reduced sensitivity
Spain	E. acervulina, E. tenella and E. maxima	50 ppm	susceptible
Lithuania	E. acervulina, E. tenella ,	50 ppm	susceptible
	E. mitis,		
	E. necatrix,		
	E.preacox and E. maxima		

Toxicity studies

In 2004, the FEEDAP Panel concluded that salinomycin does not induce gene mutations in vitro and it is also not genotoxic in vivo studies i.e. a bone marrow micronucleus assay in CD-1 and NMI mice, a DNA-repair assay in rat liver and sex-linked recessive lethal mutation assay in fruit flies. A two-year chronic toxicity studies in rats and mice confirmed that salinomycin is not carcinogenic (EFSA, 2004).

CoxRival®Salinomycin toxicity can affect cardiovascular system including high blood pressure, weakness and myocardial degeneration. Neurotoxic effects cause myelin loss, primary axonal degeneration and Wallerian-like degeneration. As a result, neurological signs such as ataxia, paralysis were observed in non-target animal dose below the maximum dose authorized for chicken.

Among birds raised for meat consumption, turkeys are extremely sensitive to CoxRival®Salinomycin toxicity. The first case report was described in 1982 when salinomycin was suspected to cause high mortality rate and low production in turkey breeder over 2 years. The investigation was done using various dose of salinomycin (27, 24, 56 mg/kg feed). The clinical signs, such as dyspnea, ataxia were shown and turkeys died in 5 to 12 h with high mortality rate (23, 34, 90%) respectively (Halvorson et al., 1982). Other reports have shown low mortality rate in turkeys (1-21%) at the concentration below 30 mg/kg feed (Andreasen & Schleifer, 1995; Stuart, 1983). Toxicity level of salinomycin is depended on age of turkey. At the dose of 22 ppm, it depressed growth rate in younger turkeys but increased mortality at older ages (Potter et al., 1986). Even though toxicity of salinomycin to turkeys was acknowledge, several cases has been reported due to the accidental feeding of commercial feed containing salinomycin sodium (Van Assen, 2006; Srinivasan et al., 2013)

Metabolic fates of CoxRival®Salinomycin in laboratory animals are acceptable to have an equivalent degree of commonality. For this reason, the data of toxic studies in laboratory animal can represent a toxicological assessment in human. The no observed adverse effect level (NOAEL) of 0.5 mg/kg bodyweight per day was determined from a one-year feeding study in dogs. Thus, a safe dose of 300 µg CoxRival®Salinomycin per day is derived for a person weigh 60 kg, corresponding to an acceptable daily intake (ADI) of 0.005 mg/kg bodyweight by applying a safety factor of 100.

Withdrawal time of CoxRival®Salinomycin has been reduced due to the supportive data based on metabolic studies with more accurate analysis method. At the present time, 24 h withdrawal time is practical use in chickens. The theoretical exposure of the consumer has been calculated according to daily human food consumption values set by Directive 2001/79/EC and the highest residue levels in tissues of animals administered the maximum dose proposed for use, measured at different withdrawal times.

As shown in table 6, the recent study revealed that after ingestion of the highest dose (70 mg/kg feed), the determined TRC at 1 h withdrawal period complied with an ADI ADI (241 mg ~80% of the ADI). The 1 h withdrawal time is considered equivalent to a zero-day withdrawal time. Accordingly, the FEEDAP Panel has proposed that a withdrawal time and maximum residue limits (MRLs) are not considered necessary (EFSA, 2017).

Table 6. Consumer theoretical exposure to Sal total residue concentrations (TRCs) in chicken tissues after 1 hour withdrawal

	Liver	Kidney	Muscle	Skin/Fat
TRC (mg/kg)	1.48	0.183	0.027	0.156
DITR* (mg)	0.206	0.003	0.011	0.021
% ADI	68	1	4	7

*Daily intake of total residues

Safety for the environment

Based on the metabolic fate data, CoxRival®Salinomycin is rapidly metablised and excreted and unchanged salinomycin amounts to 1% of the salinomycin-related products in the excreta. Salinomycin and its metabolits in chicken excreta would show less than 20% ionophoric activity (Dimenna et al., 1989). In a good practice poultry farm, diluting manure with adding soil can attenuate any potential toxic levels of salinomycin in manure. Composting manure prior to land application further also reduces s any risk of environmental contamination (Kadykalo, 2018). The recent assessment from the FEEDAP also concluded that the use of salinomycin sodium in feed for chickens will not cause a risk for aquatic environment. A risk for the terrestrial ecosystem is not considered due to the rapid metabolism and degradation of salinomycin (EFSA, 2017).

Drug resistance

The use of medicated feed in controlling of coccidiosis in broiler production has been practical for years. This situation lead to the development of drug resistance to Eimeria spp. The first resistance to salinomycin was reported in the US in 1989 by Jeffer, taken around 16 year after the discovery. After that, occurances of Eimeria spp. Resistant to salinomycin were reported from a various regions including Germany, India, and Pakistan (Stephan et al., 1997; Yadav & Gupta, 2001; Abbas et al. 2008). Recently, salinomycin was reported to be partially resistant in Iran (Arabkhazaeli et al., 2013). A variety of biochemical properties of the parasite membrane may be involved in the development of resistance against ionophores. Eimeria strains may change permeability of their cell membrane to prevent the cation transportation into cell by ionophores (Abbas et.al, 2011).

The most concern about drug resistance in ionophores including CoxRival®Salinomycin is cross resistance which is the resistance among different anticoccidial drugs having similar mode of action. It means that that Eimeria strain resistant to one ionophore will resistant to the others. A high degree of cross resistance has been reported among maduramicin, monensin, salinomycin, narasin, and lasalocid (Raether & Paeffgen, 1989). Parasites develop resistance to ionophores lower than chemicals drugs. However, the consistent use of only one drug in a farm for long term made the high risk from resistant of coccidia. In order to diminish the emergence of drug resistance, different strategies in given anticoccidial drugs were applied to control coccidiosis in poultry farm. Broilers were normally fed with medicated feed in starter and grower period. In shuttle programs, two or more anticoccidial drugs were used. A drug from one category is used for the starter period followed by a drug from a different category or a different mode of action will be used for the grower period. In rotation program, different categories of drug are used in successive flocks. Additionally, coccidiosis vaccine can be add in the rotation program (Quiroz-Castañeda & Dantán-González, 2015).

The use of vaccination and restoration of drug sensitivity

Nowadays, the global poultry industry is confronting drug resistance problems. Besides anticoccidial drugs, vaccines has been used more in poultry production to prevent and control coccidiosis. Vaccination strategy has become common to control coccidiosis in breeders and replacement layer pullets. However, the use of vaccination in broiler is still limited due to some considerations, such as high cost, administration techniques, and reversal of virulence. In addition, immunity against Eimeria is species-specific, each commercial vaccine will only protect against the included species (Chapman, 2000). To control coccidiosis in broiler, effects on broiler health and growth performance between vaccination and anticoccidial drug strategies are still in discussion. Brown (2007) reported that after infection with three species of Eimeria (E. maxima, E. acervulina, and E. tenella) in broilers, lower lesion score in the intestine of salinomycin-fed chickens was found compared with chickens vaccinated with live vaccine. Comparison of these two strategies on broiler growth performance is controversial. Several studies reported that broilers given salinomycin had better weight gain and FCR than vaccinated broilers in the starter and grower periods. But the growth rate of vaccinated group was compensatory improved during the finisher period which the weight gain and FCR was observed to be equivalent to or greater than that of salinomycin-fed groups (Lee et al., 2009; Lee et al., 2013; Lehman et al., 2009; Williams & Gobbi, 2002).

When drug resistance occurred in the farm, drug-resistant strains stay in the environment and poultry house. To solve this problem, an introduction of drug-sensitive strains into the houses was a proper solution. The drug-resistant strains in will be replaced by drug-resistant strains which can be achieved by the use of some coccidiosis live vaccines, or by the use of drug-sensitive laboratory maintained strains.

In case of salinomycin resistance, an increase in the sensitivity of field strains of Eimeria was reported following the use of live coccidiosis vaccine. Under the field condition, the Eimeria oocyst from a farm using vaccination presented a better sensitivity to salinomycin than a farm using anticoccidial drug (Jenkins et al., 2010). Chapman and Jeffers (2015) demonstrated that Eimeria isolates were partially resistant to drugs after five successive flocks were given only salinomycin. The control method was changed to vaccine in the sixth flocks and Eimeria isolates from this flock showed an increase of drug sensitivity. The present results supported that the introduction of drug-sensitive isolates from live vaccine can repopulate and replace of drug-resistant isolates in the poultry house.

Drug interaction

The severe interactions from the combination of tiamulin (used therapeutically against infections with Mycoplasma spp.) and inophores are well known in chicken. the nature of this interaction was concluded that tiamulin reduced metabolic degradation and excretion of ionophore in chickens and led to an overdosing effect (Meingassner et al.,1979) . The clinical signs (loss of appetite, locomotor disturbances, ataxia, and neurotoxicity) found after administration CoxRival®Salinomycin at use levels together with tiamulin. were associated with disturbances in the transport of ions (i.e., sodium, potassium, calcium) between myocytes and intercellular space. Histological and ultrastructural examination of muscle tissues in broilers after administration salinomycin at normal use levels together with tiamulin at 20 mg/kg bodyweight revealed myopathies and cardiomyopathies (Islam et.al, 2009). It can be concluded that tiamulin should not be used with the ionophore anticoccidials monensin, salinomycin.

Summary

To control coccidiosis in chicken production, anticoccidial drugs in feed have been extensively used for years. One of the most common drugs used in chicken farms is CoxRival®. It is a polyether carboxylic ionophore agent that has both antibacterial and anticoccidial activity. Mechanism of CoxRival®Salinomycin was related to the interfering the ion balance in parasite cell. CoxRival®Salinomycin can be used for control coccidiosis effectively. Some drug resistance were report in several countries. However, vaccination was confirmed to solve this problem. There is no risk to consumer safety because chicken can rapidly excrete CoxRival®Salinomycin and its derivatives from the body within 0.25 day after feeding. Although CoxRival®Salinomycin may be a good choice for use in chicken farm, the continuous use of only CoxRival® in the flocks should be avoided. Other drugs with distinct mechanism or other anticoccidial drug program should be applied to minimize the risk of drug resistance in the future.

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